REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of a formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-33 were pending in this application and were rejected on various grounds. With this amendment, Claim 33 has been canceled without prejudice and Claim 28 has been amended to clarify what Applicants have always regarded as their invention. The amendments to the specification and claims are fully supported by the specification and claims as originally filed and do not constitute new matter.

Claims 28-32 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Information Disclosure Statement

Applicants respectfully thank the Examiner for consider the information disclosure statement filed on November 6, 2002.

Specification

As requested by the Examiner, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code, and the title of the application has been amended to recite a new, descriptive title indicative of the invention to which the claims are directed.

Further, Applicants have amended the specification to clearly recite the conditions of the deposits made under the Budapest Treaty.

Claim Rejections – 35 U.S.C. §101

Claims 28-31 and 33 are rejected under 35 U.S.C. §101 allegedly "because invention is directed to non-statutory subject matter." In particular, the Examiner asserts that "[t]he claims read on a product of nature in that the claimed antibody is not 'isolated'."

Without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Applicants have canceled Claim 33 and have amended Claim 28 (and, as a consequence, those claims dependent from the same) to recite an "isolated antibody." According to the specification, an "isolated" antibody is "one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step" (See specification, page 311, lines 30-39).

Thus, the claimed antibodies are distinguished over antibodies in nature and the amendment to Claim 28 (and, as a consequence, those claims dependent from the same) is supported by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

Claim Rejections – 35 U.S.C. §101 and §112, First Paragraph (Enablement)

Claims 28-33 stand rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well-established utility." In particular, the Examiner alleges that "the specification does not teach any significance or functional characteristics of the PRO1760 polypeptide (SEQ ID NO:376) or antibody." Regarding the adipocyte glucose/FFA uptake assay (Example 149), the Examiner alleges that "the specification does not disclose any specific resulting cell numbers or

percentages, statistical differences, or the number of repetition for the assay. Without this knowledge … one skill in the art at the time of the invention was made would not have been able to use the information obtained from this assay in a useful manner." The Examiner further asserts that "it is not clear how PRO1760, which inhibits glucose uptake as asserted by the specification, is beneficial [for the therapeutic treatment of disorders including for example, obesity, diabetes, or hyper- or hypo-insulinemia."

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claim 33 renders the rejection of this claim moot. Applicants further submit, for the reasons set forth below, that the specification discloses at least one credible, substantial and specific asserted utility for the polypeptide PRO1760 and antibodies binding to PRO1760.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention**

that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "'substantial'" utility.'" (M.P.E.P. §2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. §2107 II (B) (1) (ii)) Such a standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

Utility – Application of Standard

Applicants rely on the adipocyte glucose/FFA uptake assay (Example 149, Assay #94) for support of patentable utility. This assay was first disclosed in International Application Serial No. PCT/US00/04342, filed on February 18, 2000, the priority of which is claimed in the present application.

The adipocyte glucose/FFA uptake assay is designed to determine whether a polypeptide is capable of modulating, either positively or negatively, the uptake of glucose or free fatty acids in adipocyte cells. By making such determinations, the assay identifies polypeptides that are expected to be useful for treating disorders wherein stimulation or inhibition of glucose uptake by adipocytes is expected to be therapeutically effective. Examples of these types of disorders include obesity, diabetes, and hyper- or hypo-insulinemia.

The adipocyte glucose/FFA assay is performed as follows: primary rat adipocyte cells are plated on a 96 well plate and incubated overnight with media supplemented with PRO1760

polypeptide. After the initial overnight incubation, samples of the media are taken at hour 4 and hour 16 and residual glycerol, glucose and FFA are measured. After the hour 16 sample is taken, insulin is added to the media and the adipocytes are allowed to incubate for an additional 4 hours. After this final 4 hour incubation, another sample is taken and residual glycerol, glucose and FFA is measured again. As a control, identical incubations and samplings are performed on cells that have been incubated overnight in media initially supplemented with insulin rather than PRO1760 polypeptide. Results are scored as positive in the assay if the uptake is greater than 1.5 times (stimulatory) or less than 0.5 time (inhibitory) the uptake of the insulin control. As PRO1760 resulted in less than 0.5 the uptake of the insulin control, PRO1760 tested positive as an inhibitor of glucose/FFA uptake in adipocyte cells.

The glucose/FFA uptake assay as described in Example 149 of the instant application was also well known in the art at the time of the effective filing date of the instant application. Similar assays were commonly used to identify potential anti-diabetic agents and study the regulatory mechanisms of important molecules involved in fat cell metabolism.

For example, at the time of the effective filing date of the instant application, it was well known in the art that increasing glucose uptake by adipocyte cells is a hallmark of a number of therapeutically effective agents, such as troglitazone and poiglitazone. (Tafuri, *Endocrinology*, 137(11): 4706-4712 (1996); Sandouk, *et al., Endocrinology*, 133(1):352-359 (1993) - copies enclosed). Both troglitazone and poiglitazone are members of the thiazolidinedione class of compounds and have been used to effectively treat noninusulin-dependent diabetes mellitus (NIDDM), the most common form of diabetes. Both compounds function, at least in part, by increasing the number of cellular glucose transporters in order to facilitate increased glucose uptake.

Further, at the time of the effective filing date of the instant application, vanadium salts were considered as a possible treatment for diabetes, and several clinical trials had already been performed. (page 26617, right column, Goldwaser *et al.*, *J. Biol Chem.*, 274(37):26617-26624 (1999) - copy enclosed). Using the rat adipocyte culture system similar to the system disclosed in the instant application, Goldwaser *et al.*, showed that vanadium ligand l-Glu (γ)HXM

potentiates the capacity of free vanadium ions to activate glucose uptake and glucose metabolism in rat adipocytes *in vitro* by 4-5 folds and to lower blood glucose levels in hyperglycemic rats *in vivo* by 5-7 folds. This is further evidence that at the effective filing date of the present application one skilled in the art would have reasonably expected that molecules activating glucose uptake would find utility in the treatment of diabetes and related diseases.

In addition, the investigators in Mueller *et al.*, who were interested in determining the influence of glucose uptake on leptin secretion, employed essentially the same assay to measure changes in glucose uptake after insulin exposure. (Mueller *et al., Endocrinology*, 139(2):551-558 (1998) - copy enclosed). Figure 1A shows the glucose concentrations in medium from 0-96 hours from isolated rat adipocytes in primary culture with various insulin concentrations. As indicated by the decrease in glucose in the medium in the Figure, Mueller *et al.* suggest that insulin produced a concentration-dependent increase in glucose uptake by the cultured adipocytes. Based on these experimental results, the authors stated that insulin increased leptin secretion over 96 hours, and the increase in leptin was closely related to the amount of glucose taken up by the adipocytes than to the insulin concentration, suggesting a role for glucose transport and/or metabolism in regulating leptin secretion. (See Abstract).

Using the same assay system, Mueller *et al.* further studied the effect on leptin secretion of two well-known anti-diabetic agents, metformin and vanadium, which were known to enhance the glucose uptake. (Muller *et al.*, *Obesity Research,* 8(7): 530-539 (2000) - copy enclosed). The experimental data indicated that both metformin and vanadium increased glucose uptake and inhibit leptin secretion from cultured adipocytes.

Accordingly, Applicants respectfully submit that at the effective filing date of the instant application, one of skill in the art would have reasonably accepted that various compounds, such as PRO1760, that are capable of modulating glucose uptake have a substantial, practical, real life utility. The above-mentioned studies have clearly established that the glucose/FFA uptake assay as described in the instant application is a reliable assay system to identify the therapeutic agents for treating diseases and conditions such as obesity, diabetes, hyper- or hypo-insulinemia. Therefore, Applicants respectfully submit that a variety of real-life utilities, such as treatments

for glucose uptake related diseases, including obesity and diabetes, are envisioned for PRO1760 and its antibody based on the glucose/FFA uptake assay results disclosed herein.

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the polypeptide PRO1760. Accordingly, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101..

Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed antibodies. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection under 35 U.S.C. §112, first paragraph.

Claim Rejections – 35 U.S.C. §112, Second Paragraph

Claims 28-33 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that "[i]t is not clear what each claim is meant to encompass given that neither the art nor the specification provide a clear definition for, or distinction between , 'binds' and 'specifically binds'".

Without acquiescing to the Examiner's position in the current rejection and solely in the interest of expediting prosecution in this case, Claim 33 has been canceled and Claim 28 (and, as a consequence, those claims dependent from the same) has been amended to recite "specifically binds". Applicants submit that the art-recognized meaning of "specific" binding is that the antibody that specifically binds to a particular antigen does not significantly cross-react with another antigen. Therefore, the term "specifically binds" in Claim 28 (and, as a consequence, those claims dependent from the same) clearly refers to an antibody that is able to bind to the polypeptide of SEQ ID NO:376 without significantly cross reacting with another antigen. Accordingly, one skilled in the art would clearly know what the scope of the invention is, and the present rejection should be withdrawn.

CONCLUSION

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C41**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: January 10, 2005

By: _____
Anna L. Barry (Reg. No. 51,436)

HELLER EHRMAN WHITE & McAULIFFE LLP
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2092289 v1